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SENT VIA UNITED PARCEL SERVICE

OCT 22 1999

Dockets Management Branch
Food and Drug Administration
HFA No. 305, Room No. 1061
5630 Fishers Lane
Rockville, MD 20852

Dear Sir/Madam:

Re: Docket No. 99D-2635

Reference is made to the FDA Draft Guidance entitled, "ANDAs: Blend Uniformity Analysis," which was published in the Federal Register on August 27, 1999.

Astra Pharmaceuticals and Zeneca Pharmaceuticals has reviewed this draft document; our comments are attached.

Please do not hesitate to contact me should you require clarification on any of the above comments.

Sincerely,

Louis E. Kornfeld for

Robert Castor
Technical Regulatory Leader
Chemistry, Manufacturing, and Controls
Regulatory Affairs Department
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RC/CSF/jr
Enclosure

99D-2635

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Astra Pharmaceuticals and Zeneca Pharmaceuticals Comments on , "ANDAs: Blend Uniformity Analysis"

General Comments

The science behind blend uniformity analysis (BUA) is complicated and we appreciate that the Agency is attempting to clarify the issues related to this important subject. However, the publication of this guidance is inappropriate since the subject matter deals with principles of process science that normally fall in the cGMP realm.

We are especially concerned that the Product Quality Research Initiative (PQRI) has not had an opportunity to provide input before this guidance was published. The importance of this issue is evident in the fact that the PQRI Product Technical Committee has chosen Blend Uniformity Testing as their #1 research project. The remit of the PQRI is to provide research based solutions to quality concerns. Ideally, the PQRI should take the science initiative and work very closely with the Agency on guidance that deals with subjects related to their research efforts.

The guidance establishes the necessity for BUA in-process testing based upon the content of 21 CFR 211.110(a). This section of the CFR references, "Such control procedures... where appropriate...". Justifying the need for BUA testing based upon the CFR alone is a sweeping conclusion. In-process tests are not necessary when a validated, well developed process exists that ensures a consistent product. The cGMPs themselves establish the principles of process validation. The result of requiring BUA is that industry will be adding an additional release requirement for products in question. This is cumbersome and unnecessary.

There are serious science issues surrounding the sampling techniques employed for powder beds. Use of a thief sampler tends to segregate the material and the resultant sample is not truly representative of the total blend. Sample sizes representing 1-3 times the dosage weight are often such a small part of the total blend, that the sample is inherently biased and shows little correlation with the true uniformity in the total blend. In addition, sampling errors and assay variance add to and multiply the chance that the thief sample misrepresents the total blend. A well known text on this subject, *Particle Size Measurement* (Chapman and Hall, NY, NY; 4th Edition, 1990) by T. Allen supports these statements and makes suggestions for alternative sampling procedures.

There are no provisions for the fact that blends will behave differently at various stages. For example, it is extremely difficult to correlate homogeneity of a tablet/capsule mass to homogeneity of the finished product. This is probably due to transportation of the tablet/capsule mass from the mixer to the final dose dividing stations, which involves multiple mechanisms that could result in segregation and/or remixing of the mass. Thus, the dose homogeneity of a tablet/capsule product should be evaluated by testing the final product.

The proposed acceptance criteria for this testing needs to be re-examined. If a sponsor chooses to sample more than six times, there should be a less stringent criterion for the stated relative standard deviation (RSD). Further, the imposition of a criterion on the mean of the blend sample seems inconsistent since the final product stage will properly demonstrate measured potency or not. Finally, the acceptance criteria section discourages the use of a two-tier system. If a blend sample fails, extended testing of the product should occur, otherwise unnecessary waste will occur.

In addition to the scientific concerns surrounding thief sampling, use of this method may violate the principles which the sampling supposedly upholds—the cGMPs. According to 21 CFR 211.160(b), laboratory controls, "...shall include the establishment of scientifically sound...sampling plans..." Paragraph (1) requires that samples "be representative and adequately identified." The guidance makes no provision for alternatives to BUA, such as monitoring of sampling time, which may fulfill the cGMP requirement and satisfy the scientific question posed.

Finally, the economic price of this testing will be high. Industry will incur costs for additional time spent by analytical and quality control/assurance personnel. Thief sampling errors will lead to rejection of blend batches resulting in significant economic loss. An additional concern will be the time that it will take to produce a batch in final market form. The consumer will ultimately suffer the consequences.

We would like to propose that the Agency revisit the science behind the idea of blend uniformity analysis in a forum with Industry representation and the PQRI. Once the science behind the issues are agreed upon the value, scope, and content of a guidance should be re-evaluated.

Specific Comments

II Scope, page 2, first paragraph- The guidance states that, "USP requires this test when the drug product contains less than 50 milligrams of the active ingredient per dosage form unit, **OR** when the active ingredient is less than 50 percent of the dosage form unit by weight." Please correct the "or" statement above with "and". This will help clarify the interpretation of Attachments A and B.

II Scope, page 2, first and second paragraph- The test for content uniformity is subject to revision within the ICH Q6A Working Group for International Harmonization. The first two paragraphs under "Scope" should reflect this agreement (i.e., number of mg per dosage unit and dosage forms requiring content uniformity testing).

II Scope, page 2, second paragraph- BUA is recommended for, "coated tablets, other than film coated tablets." It may be appropriate to distinguish between film coated tablets and coated tablets other than film coated when discussing content uniformity of the dosage units. However, when considering analysis of homogeneity of the blend, there should not be any difference between blends to be used for un-coated, film coated, or other than film coated tablets.

II Scope, page 3- The guidance states that, "An applicant should not submit a supplemental application requesting the deletion of BUA testing from commercial batches when the BUA test is also used to ensure compliance with CGMPs". Why should the Agency place a restriction on whether or not a sponsor submits an sNDA? If the sponsor has ample statistical justification for eliminating BUA and/or offers alternative testing for a specific product, then that sponsor should be granted the right of a scientific review of their proposal.

III Sampling Size and Procedures, page 3, second paragraph- The guidance states that, "For more than one drum or blender, analysis from each...". More than one blender is not normally used and we recommend deleting this reference.

IV Acceptance Criteria and Analytical Procedures, page 4- If the acceptance criteria limits given are not met, please clarify if the blend can be re-worked.

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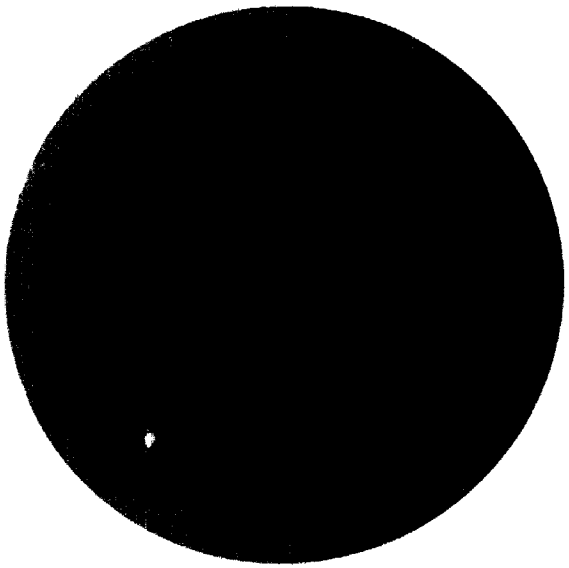

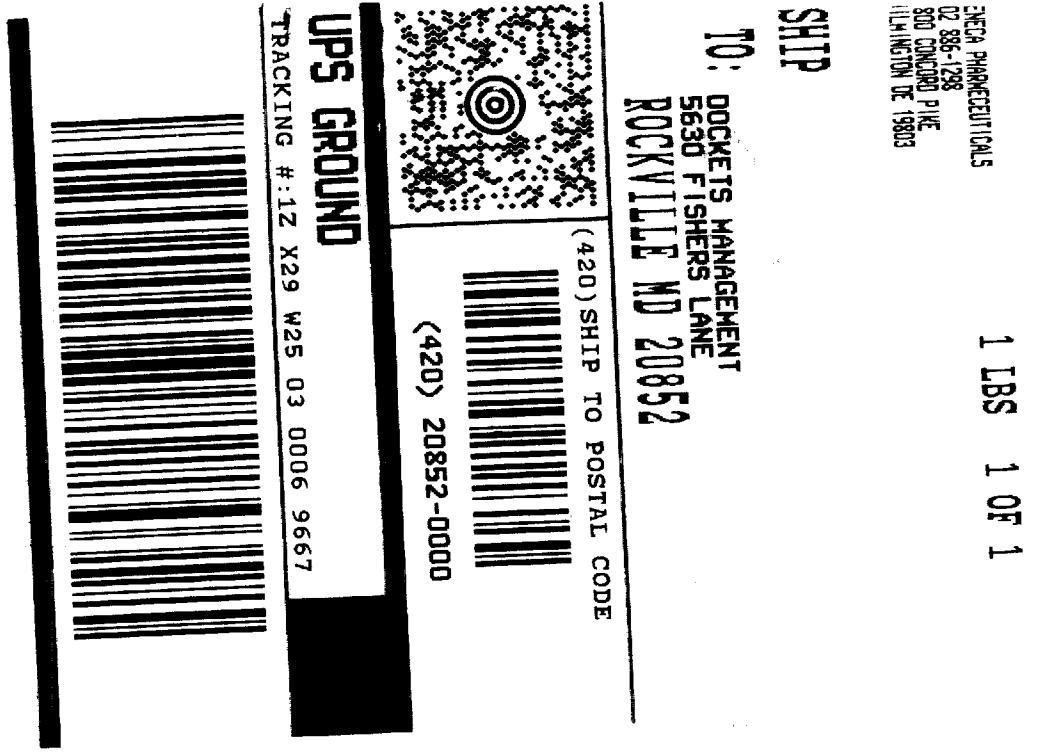

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